

### REMARKS

Reconsideration of the Examiner's rejection of the present application is respectfully requested in view of the above amendment and the following remarks.

### STATUS OF THE CLAIM(S)

Claim 5, as amended in Applicants' Amendment and Response filed June 3, 2009, was pending at the time of the Instant Office Action. In the Instant Response claim 5 has been amended. No new matter has been added by this amendment. Accordingly, claim 5 is now presented for review.

### CLAIM AMENDMENT(S)

Claim 5 is amended in order to accommodate the request by the Examiner to manifest the desired synergistic result (see the Instant Office Action at page 3, lines 5-8). Thus claim 5 has been amended to read on a *cardioprotective* pharmaceutical preparation

The Instant Amendment is submitted without waiver or prejudice to Applicants' right to pursue any subject matter cancelled thereby in one or more continuing application(s).

### SUMMARY OF OFFICE ACTION

Claim 5 stands rejected under 35 U.S.C. §103(a) as being unpatentable over Brendel et al., (US Patent No. 6,531,495, hereinafter Brendel '495), in view of Smith et al. (US Patent Pub. No. 2002/0161018, hereinafter Smith). The rejection is respectfully traversed.

### DISCUSSION

The rejection under 35 U.S.C. §103(a)

Claim 5 is drawn to the specific combination of the compound of Example 1 (i.e., 2'-{[2-(4-methoxyphenyl)acetylamino]methyl}biphenyl-2-carboxylic acid (2-pyridin-3-ylethyl)amide) with ibutilide and with dofetilide. Although Claim 5 stands rejected under 35 U.S.C. §103(a), as explained in detail in Applicants' prior Amendments and Response to Office Action (see, e.g., the Amendment and Response to Office Action submitted April 17, 2008) and acknowledged by the Examiner in prior Office Actions (see, e.g., the Office Action that issued December 4, 2008), there is sufficient evidence provided in the specification itself to demonstrate unexpected synergism for the combination of the compound of Example 1 with ibutilide and with dofetilide. Further, as agreed with the Examiner during the June 1, 2009, teleconference, claim 5 has been limited to (a) intravenous formulations containing (b) synergistic amounts of the component active ingredients which (c) deliver a clearly synergistic amount of the compound of Example 1; i.e., from 0.3 mg/kg/hr to about 3 mg/kg/hr.

In the Instant Office Action it is alleged that despite Applicants' June 3, 2009, Amendment claim 5 still suffers from two deficiencies, as follows:

- (1) a range is not provided for each of ibutilide and dofetilide over which a synergistic effect is obtained in combination with the compound of Example 1; and
- (2) the claim does not state the desired synergistic result of the claimed pharmaceutical preparation.

Taking the second alleged deficiency first, without acceding to the correctness of the Examiner's position and solely to facilitate advancement of the Instant Application toward allowance, with the Instant Amendment Applicants have adopted the Examiner's suggested language and amended claim 5 in order to clarify that the claimed subject matter relates to "a cardioprotective pharmaceutical preparation"; (see the Instant Office Action at page 3, lines 6-7). As such the Instant Amendment renders moot the second alleged deficiency.

Regarding the first alleged deficiency, Applicants respectfully traverse the assertion that the information disclosed in the application does not sufficiently distinguish and support the scope of synergistic combinations that are currently encompassed by claim 5. Applicants note the following remarks, which appears in the Instant Office Action in the paragraph bridging pages 2-3 therein:

Examiner notes, claims drawn to (unexpectedly) synergistic combinations of known ingredients must be factually supported by data commensurate in scope with the claims. See, In re Kollman, 201 USPQ 193 (C.C.P.A. 1979) [595 F.2d 48; 1979]. (The court affirming a 103 rejection of a claim containing the word "synergistic", because the claims were not commensurate in scope with the showing of unexpected results, other than at 1:1 ratio for certain specific combinations). Here, while rate of administration for the phenyl carboxamide compound is disclosed, it is unclear what dosage range of ibutilide or dofetilide [sic] in combination shows a synergistic effect.

(emphasis added).

Applicants respectfully suggest that the holding in In re Kollman was more narrow than is suggested by the foregoing. In particular, the court in In re Kollman did not hold, as the above-quoted passage appears to imply, that a claimed range cannot exceed the bounds of the data demonstrating a synergistic effect. Indeed the court in In re Kollman held to the contrary, as shown by the following extended excerpt therefrom:

The next point at issue concerns the scope of proof offered in support of these claims.

Claims 6, 7 and 8 all require a FENAC/diphenyl ether ratio ranging between 1:1 and 4:1. Tables I, II and III (footnotes 3, 4 and 5, supra) provide data for a range of 1:1 to 2:1 for the composition of claim 6 (containing ether I) and a range of 2:1 to 4:1 for the compositions of claims 7 and 8 (containing ethers II and III respectively). The solicitor argues that the lack of data for the remainder of the claimed ranges mandates an affirmance of the board's decision [to reject all claims].

We feel that the unobviousness of a broader claimed range can, in certain instances, be proven by a narrower range of data. Often, one having ordinary skill in the art may be able to ascertain a trend in the exemplified data which would allow him to reasonably extend the probative value

thereof. The proof, thus considered, might then be sufficient to rebut a PTO holding of prima facie obviousness.

The data pertinent to claims 7 and 8 appear to support such an extension, those to claim 6 do not appear to do so.

First, with regard to claims 7 and 8, consider in Tables I and II in the column marked 2 lb/acre of FENAC, the three entries for each of ethers II and III. These entries -- going down the table -- are equivalent to 16:1, 8:1 and 4:1 FENAC/diphenyl ether. The effectiveness increases as it approaches the contested region of the claimed range and yet still far outstrips the additive total of "expected" effectiveness. A similar conclusion may be drawn from the entries in the column drawn to 1 lb/acre of FENAC corresponding to ratios of 8:1, 4:1 and 2:1.

On the other hand, the data in Tables I and III corresponding to claim 6 (ether I) cover only a third of the range of claim 6 (1:1 to 2:1), and *the effectiveness appears to decrease to the "expected" level as the untested region of that claimed range is approached.* For instance, the entries at 1 pound/acre of ether I at both 1 and 2 pounds/acre of FENAC, (corresponding to 1:1 and 2:1 ratios, respectively) show the effectiveness to be only 30% and to approach the expected levels of 0% to 10%. Accordingly, the data do not support the breadth of claim 6.

(In re Kollman, 595 F.2d 48; 56-57; emphasis added, footnotes omitted).

Thus it can be seen that, contrary to the Examiner's assertion that "[t]he court affirm[ed] a 103 rejection of a claim containing the word 'synergistic', because the claims were [sic, *claim was*] not commensurate in scope with the showing of unexpected results, other than at 1:1 ratio for certain specific combinations", the only rejection that the Kollman court upheld concerned a claim with respect to which the data demonstrated a *lack of synergy*.

In contrast to claim 6, the Kollman court *overturned* the rejection of claims 7 and 8, even though the experimental data did not represent the full range of the claims. Rather the Kollman

court reasoned that patentability is recognized when one having ordinary skill in the art may reasonably extend the probative value of the data presented to the range encompassed by the claimed subject matter.

As relates to the Instant Application, there are no data that present any kind of "Claim 6" problem as occurred in Kollman; i.e., none of the data provided in the Instant Application suggest a *lack* of symmetry. Nor has the Examiner presented any other reason why a person of ordinary skill in the art would doubt that the data provided in the instant specification fully support the current scope of claim 5. As such Applicants respectfully submit that claim 5, as currently amended, is patentable over Brendel '495 in view of Smith. Accordingly, Applicants respectfully request that the rejection of claim 5 under 35 USC §103(a) be withdrawn.

#### CONCLUSION

In view of the Instant Amendment and the Discussion presented herein, the Examiner is respectfully requested to reconsider and to withdraw the present rejection under 35 U.S.C. §103(a). It is submitted that the claim in the present application is now in condition for allowance, and action to that effect is respectfully requested.

The Commissioner is hereby authorized to charge any additional fees or credit any overpayment resulting from this Amendment to Deposit Account 18-1982.

Respectfully submitted,

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